

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/16007

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/68; C07H 21/04  
 US CL :435/6, 7.1, 7.23; 536/23.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 7.1, 7.23; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, WEST

search terms: p27, prostate carcinoma, beginin prostate hyperplasia.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COTE et al. Association of p27 <sup>Kip1</sup> levels with recurrence and survival in patients with stage C prostate carcinoma. J. Natl. Cancer Institute. 17 June 1998, Vol. 90, No. 12, pages 916-920. See entire document.	1, 4
X	LLOYD et al. p27 <sup>Kip1</sup> : A multifunctional cyclin-dependent kinase inhibitor with prognostic significance in human cancers. American J. Pathology. February 1999, Vol. 154, No. 2, pages 313-323. See entire document, and especially page 319, first column.	2, 3
X	US 5,688,665 A (MASSAGUE et al) 18 November 1997. See entire document.	11

Further documents are listed in the continuation of Box C.  See patent family annex.

Special categories of cited documents:	
"A" document: showing the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 AUGUST 2000

Date of mailing of the international search report

22 SEP 2000

Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MINH-TAM DAVIS

Telephone No. (703) 308-0916



# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US00/16007

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-4, 11

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International Application No.

PCT/US00/16007

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-4 and 11 drawn to a method of diagnosis of prostate carcinoma, or benign hyperplasia, by detecting p27, and a composition comprising a nucleic acid molecule encoding p27 for treating said cancer.

Group II, claim 14, drawn to a method for determining the rate of proliferation of a prostate cancer, by detecting p21.

Group III, claims 5-8, drawn to a method of treating prostate cancer, by administering a nucleic acid molecule encoding p27

Group IV, claim 9, drawn to a method of treating prostate cancer, by administering p27 protein.

Group V, claim 10, drawn to a method of treating prostate cancer, by administering a substance capable of stabilizing p27 protein.

Group VI, claim 12, drawn to a composition comprising p27 protein.

Group VII, claim 13, drawn to a substance capable of stabilizing p27 protein.

Group VIII, claim 15, drawn to a method of determining the rate of proliferation of a prostate cancer, by detecting the mdm2 expression.

Group IX, claims 16 and 17, drawn to a method of diagnosis of metastasis of a prostate cancer, by determining the level of cyclin D1 expression.

Group X, claim 18, drawn to a method for determining tumor recurrence, by detecting p16.

Group XI, claims 19-24, drawn to method of treating prostate cancer, by administering anti-Her-2/neu antibody.

Group XII, claims 25-26, drawn to a method for diagnosis of prostate cancer, by measuring Her-2/neu expression.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

Group I, species detection of prostate carcinoma, and prostate hyperplasia.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-XII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

An international stage application shall relate to one invention only or to a group of invention so linked as to form a single general inventive concept. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475 (d)).

Group I, claims 1-4, 11, form a single inventive concept of a method of diagnosis of prostate cancer, by detecting p27 protein or mRNA, or both, and a composition comprising a nucleic acid molecule encoding p27 protein.

Group II, claim 14, is an additional method, method of determining the rate of prostate cancer proliferation, by detecting p21 protein. Group II is distinct from group I, because the reagents used in group II is different from that of group I, i.e. using p27 versus p21 protein. Furthermore, since p27 is known in the art (US 5688665), p27 is not novel to form a link for a single general inventive concept.

Group III, claims 5-8, is an additional method of use for the claimed p27, i.e. treating a patient by administering a p27 polynucleotide. The objective, and the means of the method of group III is distinct from those of group I, i.e. treating prostate cancer versus diagnosis of cancer, and administration of p27 polynucleotide versus detection of the expression p27.

Group IV, claim 9, is an additional method of use for the claimed p27, i.e. treating a patient by administering a p27 protein. The objective of group IV is distinct from that of group I, i.e. treating prostate cancer versus diagnosis of cancer. Furthermore, the mean of the method of group IV is distinct from those of groups I and III, i.e. administering p27 protein versus detecting the presence of p27, and administering p27 polynucleotide, respectively.

Group V, claim 9, is an additional method of use, i.e. treating a patient by administering a substance capable of stabilizing p27 protein. The objective of group V is distinct from that of group I, i.e. treating prostate cancer versus diagnosis of cancer. Furthermore, the mean of the method of group V, i.e. administering a substance capable of stabilizing p27 protein, is distinct from those of groups I, III, and IV, i.e. detecting the presence of p27, administering p27 polynucleotide, and

**INTERNATIONAL SEARCH REPORT**

International Application No.

PCT/US00/16007

administering p27 protein, respectively.

Group VI, claim 12, drawn to p27 protein, which is structurally distinct from p27 polynucleotide of group I.

Group VII, claim 13, drawn to a substance capable of stabilizing p27 protein, which is structurally distinct from p27 polynucleotide of group I.

Group VIII, claim 15, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting mdm2 expression versus detecting p27 expression of group I.

Group IX, claims 16, 17, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting cyclin D1 expression versus detecting p27 expression of group I.

Group X, claim 18, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting p16 expression versus detecting p27 expression of group I.

Group XI, claims 19-24, is an additional method of use, which is distinct from the method of group I by using different means, i.e. administering an anti-Her-2/neu antibody versus detecting p27 expression of group I.

Group XII, claims 25-26, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting expression of Her-2/neu versus detecting p27 expression of group I.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The species of group I are distinct from each other because prostate carcinoma and benign prostate hyperplasia are different diseases, and thus the objectives of the diagnosis of the two species are distinct.

## PCTENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

Date of mailing (day/month/year)

20 March 2001 (20.03.01)

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

International application No.

PCT/US00/16007

Applicant's or agent's file reference

55293-B-PCT/JPW/EMW

International filing date (day/month/year)

09 June 2000 (09.06.00)

Priority date (day/month/year)

10 June 1999 (10.06.99)

Applicant

CORDON-CARDO, Carlos et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

05 January 2001 (05.01.01)



in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Claudio Borton

Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) 55293-B-PCT/JPW/EMW

Box No. I TITLE OF INVENTION  
MARKERS FOR PROSTATE CANCER

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH  
1275 York Avenue  
New York, New York 10021  
United States of America

This person is also inventor.

Telephone No.

None

Facsimile No.

None

Teleprinter No.

None

State (that is, country) of nationality:  
United States of America

State (that is, country) of residence:  
United States of America

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CORDON-CARDO, Carlos  
860 U.N. Plaza  
Apt. 14F  
New York, New York 10017  
United States of America

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
United States of America

State (that is, country) of residence:  
United States of America

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

agent

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WHITE, John P.  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, New York 10036  
United States of America

Telephone No.

(212) 278-0400

Facsimile No.

(212) 391-0526

Teleprinter No.

None

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

See Notes to the request form

## Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SCHER, Howard I.  
264 Highwood Avenue  
Tenafly, New Jersey 07670  
United States of America

This person is:

applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
United States of America

State (that is, country) of residence:  
United States of America

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KOFF, Andrew  
593 Cathleen Place  
Westbury, New York 11590  
United States of America

This person is:

applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
United States of America

State (that is, country) of residence:  
United States of America

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

applicant only  
 applicant and inventor  
 inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

Further applicants and/or (further) inventors are indicated on another continuation sheet.

## Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

## Regional Patent

AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

<input type="checkbox"/> AE United Arab Emirates	<input type="checkbox"/> LR Liberia
<input type="checkbox"/> AL Albania	<input type="checkbox"/> LS Lesotho
<input type="checkbox"/> AM Armenia	<input type="checkbox"/> LT Lithuania
<input type="checkbox"/> AT Austria	<input type="checkbox"/> LU Luxembourg
<input type="checkbox"/> AU Australia	<input type="checkbox"/> LV Latvia
<input type="checkbox"/> AZ Azerbaijan	<input type="checkbox"/> MA Morocco
<input type="checkbox"/> BA Bosnia and Herzegovina	<input type="checkbox"/> MD Republic of Moldova
<input type="checkbox"/> BB Barbados	<input type="checkbox"/> MG Madagascar
<input type="checkbox"/> BG Bulgaria	<input type="checkbox"/> MK The former Yugoslav Republic of Macedonia
<input type="checkbox"/> BR Brazil	<input type="checkbox"/> MN Mongolia
<input type="checkbox"/> BY Belarus	<input type="checkbox"/> MW Malawi
<input checked="" type="checkbox"/> CA Canada	<input type="checkbox"/> MX Mexico
<input type="checkbox"/> CH and LI Switzerland and Liechtenstein	<input type="checkbox"/> NO Norway
<input type="checkbox"/> CN China	<input type="checkbox"/> NZ New Zealand
<input type="checkbox"/> CR Costa Rica	<input type="checkbox"/> PL Poland
<input type="checkbox"/> CU Cuba	<input type="checkbox"/> PT Portugal
<input type="checkbox"/> CZ Czech Republic	<input type="checkbox"/> RO Romania
<input type="checkbox"/> DE Germany	<input type="checkbox"/> RU Russian Federation
<input type="checkbox"/> DK Denmark	<input type="checkbox"/> SD Sudan
<input type="checkbox"/> DM Dominica	<input type="checkbox"/> SE Sweden
<input type="checkbox"/> EE Estonia	<input type="checkbox"/> SG Singapore
<input type="checkbox"/> ES Spain	<input type="checkbox"/> SI Slovenia
<input type="checkbox"/> FI Finland	<input type="checkbox"/> SK Slovakia
<input type="checkbox"/> GB United Kingdom	<input type="checkbox"/> SL Sierra Leone
<input type="checkbox"/> GD Grenada	<input type="checkbox"/> TJ Tajikistan
<input type="checkbox"/> GE Georgia	<input type="checkbox"/> TM Turkmenistan
<input type="checkbox"/> GH Ghana	<input type="checkbox"/> TR Turkey
<input type="checkbox"/> GM Gambia	<input type="checkbox"/> TT Trinidad and Tobago
<input type="checkbox"/> HR Croatia	<input type="checkbox"/> TZ United Republic of Tanzania
<input type="checkbox"/> HU Hungary	<input type="checkbox"/> UA Ukraine
<input type="checkbox"/> ID Indonesia	<input type="checkbox"/> UG Uganda
<input type="checkbox"/> IL Israel	<input type="checkbox"/> US United States of America
<input type="checkbox"/> IN India	continuation-in-part (see Page 5)
<input type="checkbox"/> IS Iceland	
<input checked="" type="checkbox"/> JP Japan	
<input type="checkbox"/> KE Kenya	
<input type="checkbox"/> KG Kyrgyzstan	
<input type="checkbox"/> KP Democratic People's Republic of Korea	
<input type="checkbox"/> KR Republic of Korea	
<input type="checkbox"/> KZ Kazakhstan	
<input type="checkbox"/> LC Saint Lucia	
<input type="checkbox"/> LK Sri Lanka	

UZ Uzbekistan

VN Viet Nam

YU Yugoslavia

ZA South Africa

ZW Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

.....

.....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

See Notes to the request form

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claim information is contained in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 10.06.99 (10 June 1999)	09/329,917	US		
item (2)				
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

## Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):	Request to use results of earlier search: reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
	Date (day/month/year)	Number	Country (or regional Office)
ISA / US			

## Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:	This international application is accompanied by the item(s) marked below:	
request : 6	<input checked="" type="checkbox"/> fee calculation sheet	
description (excluding sequence listing part) : 104	<input type="checkbox"/> separate signed power of attorney	
claims : 4	<input type="checkbox"/> copy of general power of attorney: reference number, if any:	
abstract : 1	<input type="checkbox"/> statement explaining lack of signature	
drawings : 14	<input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):	
sequence listing part of description : 0	<input type="checkbox"/> translation of international application into (language):	
Total number of sheets : 129	<input type="checkbox"/> separate indications concerning deposited microorganism or other biological material	
	<input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form	
	<input checked="" type="checkbox"/> other (specify): Transmittal Letter, Attachment A	

Figure of the drawings which  
should accompany the abstract: Language of filing of the  
international application: English

## Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

NAME: James S. Quirk

DATE

7/25/03

TITLE: Senior Vice-President, Research Resources Management

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	<input type="checkbox"/> received: <input type="checkbox"/> not received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy  
by the International Bureau:

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claim(s) are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 10.06.99 (10 June 1999)	09/329,917	US		
item (2)				
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

## Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

## Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	6
description (excluding sequence listing part)	:	104
claims	:	4
abstract	:	1
drawings	:	14
sequence listing part of description	:	0
Total number of sheets :		129

This international application is accompanied by the item(s) marked below:

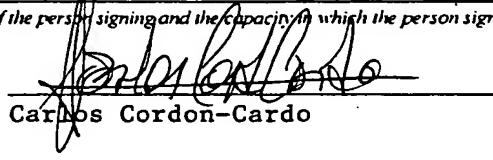
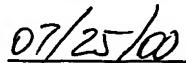
1.  fee calculation sheet
2.  separate signed power of attorney
3.  copy of general power of attorney: reference number, if any:
4.  statement explaining lack of signature
5.  priority document(s) identified in Box No. VI as item(s):
6.  translation of international application into (language):
7.  separate indications concerning deposited microorganism or other biological material
8.  nucleotide and/or amino acid sequence listing in computer readable form
9.  other (specify): Transmittal Letter, Attachment A

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

## Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Date

Howard I. Scher

Date

Andrew Koff

Date

For receiving Office use only

1. Date of actual receipt of the purported international application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /

6.  Transmittal of search copy delayed until search fee is paid.

2. Drawings:

received:

not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claim(s) made in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 10.06.99 (10 June 1999)	09/329,917	US		
item (2)				
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

## Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / US	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) _____ Number _____ Country (or regional Office) _____
--	---

## Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:  request : 6 description (excluding sequence listing part) : 104 claims : 4 abstract : 1 drawings : 14 sequence listing part of description : 0  Total number of sheets : 129	This international application is accompanied by the item(s) marked below:  1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): Transmittal Letter, Attachment A
--	--

Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English
---	--

## Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Carlos Cordon-Cardo

Date

Howard I. Scher

Date

Andrew Koff

Date

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings:  <input type="checkbox"/> received:  <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:
---

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claim(s) in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 10.06.99 (10 June 1999)	09/329,917	US		
item (2)				
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

## Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / US	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):
	Date (day/month/year) Number Country (or regional Office)

## Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:	This international application is accompanied by the item(s) marked below:
request : 6	1. <input checked="" type="checkbox"/> fee calculation sheet
description (excluding sequence listing part) : 104	2. <input type="checkbox"/> separate signed power of attorney
claims : 4	3. <input type="checkbox"/> copy of general power of attorney; reference number, if any:
abstract : 1	4. <input type="checkbox"/> statement explaining lack of signature
drawings : 14	5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):
sequence listing part of description : 0	6. <input type="checkbox"/> translation of international application into (language):
Total number of sheets : 129	7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material
	8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form
	9. <input checked="" type="checkbox"/> other (specify): Transmittal Letter, Attachment A
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English

## Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Carlos Cordon-Cardo

Date

Howard I. Scher

Date

Andrew Koff

Date

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	<input type="checkbox"/> received: <input type="checkbox"/> not received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

See Notes to the request form

## Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. II" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "parent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box V.: U.S. Serial No. 09/329,917, filed June 10, 1999

The demand must be filed directly with the competent International Preliminary Examining Authority. Two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

# PCT

## CHAPTER II

### DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>	
International application No. PCT/US00/16007	International filing date (day/month/year) 9 June 2000
(Earliest) Priority date (day/month/year) 10 June 1999	
Title of invention MARKERS FOR PROSTATE CANCER	
<b>Box No. II APPLICANT(S)</b>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH 1275 York Avenue New York, New York 10021 United States of America	Telephone No.: None
	Facsimile No.: None
	Teleprinter No.: None
State (i.e. country) of nationality: United States of America	State (i.e. country) of residence: United States of America
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) CORDON-CARDO, Carlos 860 U.N. Plaza Apt. 14F New York, New York 10017 United States of America	
State (i.e. country) of nationality: United States of America	State (i.e. country) of residence: United States of America
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SCHER, Howard I. 264 Highwood Avenue Tenafly, New Jersey 07670 United States of America	
State (i.e. country) of nationality: United States of America	State (i.e. country) of residence: United States of America
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.	

## Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet is not to be included in the demand.*Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KOFF, Andrew  
 593 Cathleen Place  
 Westbury, New York 11590  
 United States of America

State (i.e. country) of nationality:  
 United States of America

State (i.e. country) of residence:  
 United States of America

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (i.e. country) of nationality:

State (i.e. country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (i.e. country) of nationality:

State (i.e. country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (i.e. country) of nationality:

State (i.e. country) of residence:

Further applicants are indicated on another continuation sheet.

## Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is  agent  common representative  
 and  has been appointed earlier and represents the applicant(s) also for international preliminary examination.  
 is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.  
 is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WHITE, John P.  
 Cooper & Dunham LLP  
 1185 Avenue of the Americas  
 New York, New York 10036  
 United States of America

Telephone No.:  
 (212) 278-0400

Facsimile No.:  
 (212) 391-0526

Teleprinter No.:  
 None

Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

## Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority\*

- (i)  to start the international preliminary examination on the basis of the international application as originally filed.
- (ii)  to take into account the amendments under Article 34 of
  - the description (amendments attached).
  - the claims (amendments attached).
  - the drawings (amendments attached).
- (iii)  to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv)  to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v)  to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

## Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT) except* .....

.....

.....

*(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)*

## Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

## 1. amendments under Article 34

description : sheets  
claims : sheets  
drawings : sheets

## 2. letter accompanying amendments under Article 34

## 3. copy of amendments under Article 19

## 4. copy of statement under Article 19

## 5. other (specify):

## For International Preliminary Examining Authority use only

received  not received 

<input type="checkbox"/>	<input type="checkbox"/>

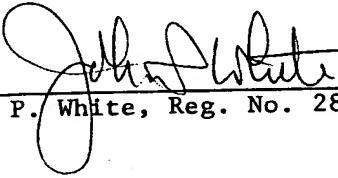
The demand is also accompanied by the item(s) marked below:

1.  separate signed power of attorney  
2.  copy of general power of attorney  
3.  statement explaining lack of signature

4.  fee calculation sheet  
5.  other (specify): Express Mail Certificate of Mailing Bearing Express Mail Label #EK873630392US dated 5 January 2001

## Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).*

  
John P. White, Reg. No. 28,678

5 January 2001  
Date

## For International Preliminary Examining Authority use only

## 1. Date of actual receipt of DEMAND:

## 2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3.  The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5. below, does not apply.

The applicant has been informed accordingly.

4.  The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended, by virtue of Rule 80.5.5.  Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

## For International Bureau use only

Demand received from IPEA on:

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/16007

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/68; C07H 21/04  
US CL :435/6, 7.1, 7.23; 536/23.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 7.1, 7.23; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, WEST  
search terms: p27, prostate carcinoma, beginin prostate hyperplasia.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COTE et al. Association of p27 <sup>Kip1</sup> levels with recurrence and survival in patients with stage C prostate carcinoma. J. Natl. Cancer Institute. 17 June 1998, Vol. 90, No. 12, pages 916-920. See entire document.	1, 4
X	LLOYD et al. p27 <sup>Kip1</sup> : A multifunctional cyclin-dependent kinase inhibitor with prognostic significance in human cancers. American J. Pathology. February 1999, Vol. 154, No. 2, pages 313-323. See entire document, and especially page 319, first column.	2, 3
X	US 5,688,665 A (MASSAGUE et al) 18 November 1997. See entire document.	11

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document: giving the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
25 AUGUST 2000	22 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MINH-TAM DAVIS Telephone No. (703) 308-0916

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/16007

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-4, 11

Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/16007

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-4 and 11 drawn to a method of diagnosis of prostate carcinoma, or benign hyperplasia, by detecting p27, and a composition comprising a nucleic acid molecule encoding p27 for treating said cancer.

Group II, claim 14, drawn to a method for determining the rate of proliferation of a prostate cancer, by detecting p21.

Group III, claims 5-8, drawn to a method of treating prostate cancer, by administering a nucleic acid molecule encoding p27

Group IV, claim 9, drawn to a method of treating prostate cancer, by administering p27 protein.

Group V, claim 10, drawn to a method of treating prostate cancer, by administering a substance capable of stabilizing p27 protein.

Group VI, claim 12, drawn to a composition comprising p27 protein.

Group VII, claim 13, drawn to a substance capable of stabilizing p27 protein.

Group VIII, claim 15, drawn to a method of determining the rate of proliferation of a prostate cancer, by detecting the mdm2 expression.

Group IX, claims 16 and 17, drawn to a method of diagnosis of metastasis of a prostate cancer, by determining the level of cyclin D1 expression.

Group X, claim 18, drawn to a method for determining tumor recurrence, by detecting p16.

Group XI, claims 19-24, drawn to method of treating prostate cancer, by administering anti-Her-2/neu antibody.

Group XII, claims 25-26, drawn to a method for diagnosis of prostate cancer, by measuring Her-2/neu expression.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

Group I, species detection of prostate carcinoma, and prostate hyperplasia.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-XII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

An international stage application shall relate to one invention only or to a group of invention so linked as to form a single general inventive concept. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475 (d)).

Group I, claims 1-4, 11, form a single inventive concept of a method of diagnosis of prostate cancer, by detecting p27 protein or mRNA, or both, and a composition comprising a nucleic acid molecule encoding p27 protein.

Group II, claim 14, is an additional method, method of determining the rate of prostate cancer proliferation, by detecting p21 protein. Group II is distinct from group I, because the reagents used in group II is different from that of group I, i.e. using p27 versus p21 protein. Furthermore, since p27 is known in the art (US 5688665), p27 is not novel to form a link for a single general inventive concept.

Group III, claims 5-8, is an additional method of use for the claimed p27, i.e. treating a patient by administering a p27 polynucleotide. The objective, and the means of the method of group III is distinct from those of group I, i.e. treating prostate cancer versus diagnosis of cancer, and administration of p27 polynucleotide versus detection of the expression p27.

Group IV, claim 9, is an additional method of use for the claimed p27, i.e. treating a patient by administering a p27 protein. The objective of group IV is distinct from that of group I, i.e. treating prostate cancer versus diagnosis of cancer. Furthermore, the mean of the method of group IV is distinct from those of groups I and III, i.e. administering p27 protein versus detecting the presence of p27, and administering p27 polynucleotide, respectively.

Group V, claim 9, is an additional method of use, i.e. treating a patient by administering a substance capable of stabilizing p27 protein. The objective of group V is distinct from that of group I, i.e. treating prostate cancer versus diagnosis of cancer. Furthermore, the mean of the method of group V, i.e. administering a substance capable of stabilizing p27 protein, is

distinct from those of groups I, III, and IV, i.e. detecting the presence of p27, administering p27 polynucleotide, and

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/16007

administering p27 protein, respectively.

Group VI, claim 12, drawn to p27 protein, which is structurally distinct from p27 polynucleotide of group I.

Group VII, claim 13, drawn to a substance capable of stabilizing p27 protein, which is structurally distinct from p27 polynucleotide of group I.

Group VIII, claim 15, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting mdm2 expression versus detecting p27 expression of group I.

Group IX, claims 16, 17, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting cyclin D1 expression versus detecting p27 expression of group I.

Group X, claim 18, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting p16 expression versus detecting p27 expression of group I.

Group XI, claims 19-24, is an additional method of use, which is distinct from the method of group I by using different means, i.e. administering an anti-Her-2/neu antibody versus detecting p27 expression of group I.

Group XII, claims 25-26, is an additional method of use, which is distinct from the method of group I by using different means, i.e. detecting expression of Her-2/neu versus detecting p27 expression of group I.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The species of group I are distinct from each other because prostate carcinoma and benign prostate hyperplasia are different diseases, and thus the objectives of the diagnosis of the two species are distinct.

JPW

## PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

WHITE, John, P.  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, NY 10036  
ETATS-UNIS D'AMERIQUERECEIVED  
COOPER & DUNHAM

received

Draft for new 1301

JAN - 2 2001

DUCKET CLERK

Date of mailing (day/month/year) 21 December 2000 (21.12.00)		RECEIVED COOPER & DUNHAM JAN - 2 2001 DUCKET CLERK	
Applicant's or agent's file reference 55293-B-PCT/JPW/EMW		IMPORTANT NOTICE	
International application No. PCT/US00/16007	International filing date (day/month/year) 09 June 2000 (09.06.00)	Priority date (day/month/year) 10 June 1999 (10.06.99)	✓
Applicant SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

CA,EP,JP

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 21 December 2000 (21.12.00) under No. WO 00/77258

## REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit. → 1/10/01 w.d. 20 mo : 2/10/01 w.d.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

## REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JOHN P. WHITE  
COOPER & DUNHAM LLP  
1185 AVENUE OF THE AMERICAS  
NEW YORK, NEW YORK 10036

JPW  
PCT

## WRITTEN OPINION

(PCT Rule 66)

20

Written Opinion 10.14.01

AP

Date of Mailing  
(day/month/year)

14 SEP 2001

Applicant's or agent's file reference  55293-B-PCT/		REPLY DUE within ONE months from the above date of mailing
International application No.  PCT/US00/16007	International filing date (day/month/year)  09 JUNE 2000	Priority date (day/month/year)  10 JUNE 1999
International Patent Classification (IPC) or both national classification and IPC IPC(7): C12Q 1/68; C07H 21/04 and US Cl.: 435/6, 7.1, 7.23; 536/23.5		
Applicant SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH		

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I  Basis of the opinion
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

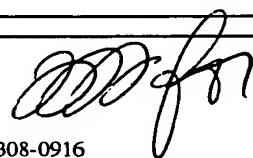
When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10 OCTOBER 2001.

Name and mailing address of the IPEA/US  Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  MINH TAM DAVIS 
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0916

## WRITTEN OPINION

International application No.

PCT/US00/16007

## I. Basis of the opinion

## 1. With regard to the elements of the international application:\*

 the international application as originally filed the description:

pages 1-104, as originally filed

pages NONE

pages NONE, filed with the demand

pages NONE, filed with the letter of \_\_\_\_\_

 the claims:

pages 105-108, as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages NONE, filed with the letter of \_\_\_\_\_

 the drawings:

pages .1-15, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of \_\_\_\_\_

 the sequence listing part of the description:

pages NONE, as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of \_\_\_\_\_

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

 the language of a translation furnished for the purposes of international search (under Rule 23.1(b)). the language of publication of the international application (under Rule 48.3(b)). the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

 contained in the international application in printed form. filed together with the international application in computer readable form. furnished subsequently to this Authority in written form. furnished subsequently to this Authority in computer readable form. The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4.  The amendments have resulted in the cancellation of: the description, pages NONE the claims, Nos. NONE the drawings, sheets/fig NONE5.  This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

## WRITTEN OPINION

International application No.  
PCT/US00/16007

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

 the entire international application. claims Nos. 5-10, 12-26

because:

 the said international application, or the said claim Nos.   relate to the following subject matter which does not require international preliminary examination (*specify*). the description, claims or drawings (*indicate particular elements below*) or said claims Nos.   are so unclear that no meaningful opinion could be formed (*specify*). the claims, or said claims Nos.   are so inadequately supported by the description that no meaningful opinion could be formed. no international search report has been established for said claims Nos. 5-10,12-26.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

 the written form has not been furnished or does not comply with the standard. the computer readable form has not been furnished or does not comply with the standard.

## WRITTEN OPINION

International application No.

PCT/US00/16007

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-4, 11</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-4, 11</u>	NO
Industrial Applicability (IA)	Claims <u>1-4, 11</u>	YES
	Claims <u>NONE</u>	NO

**2. citations and explanations**

Claims 1, 4 lacks novelty under PCT Article 33(2) as being anticipated by Cote et al.

Cote et al teach detection of p27 by immunoreactivity. Cote et al further teach that decrease p27 reactivity is significantly associated with an increased probability of recurrence and decreased survival of patients with stage C prostate carcinoma (abstract and figure 2). Cote et al further teach that 12 tumors show low or no detectable p27 reactivity, and that decreased levels of p27 are associated with tumor grade (abstract and table 1).

Claims 2,3 lack novelty under PCT Article 33(2) as being anticipated by Lloyd et al.

Lloyd et al teach that Cordon-Cardo et al observed that p27 protein and mRNA are almost undetectable in both epithelial and stromal cells of benign prostate hyperplasia (p.319, first column, second paragraph).

Claim 11 lacks novelty under PCT Article 33(2) as being anticipated by US 5,688,665 A.

US 5,688,665 A teaches nucleic acid molecules encoding p27 protein.

----- NEW CITATIONS -----

NONE

WRITTEN OPINION

International application No.

PCT/US00/16007

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**TIME LIMIT:**

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.